Exhibit 3

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

ARIA DIAGNOSTICS, INC., Plaintiff, vs. SEQUENOM, INC., Defendant.	Case No. 3:11-cv-06391-SI **DECLARATION OF DR. FARIDEH BISCHOFF IN SUPPORT OF ARIOSA DIAGNOSTICS, INC.'S OPPOSITION TO SEQUENOM, INC.'S MOTION FOR PRELIMINARY INJUNCTION** Date of Hearing: June 15, 2012 Time of Hearing: 9:00 a.m. Location: Courtroom 10 19th Floor Judge: Hon. Susan Illston
SEQUENOM, INC., Counterclaim Plaintiff, vs. ARIA DIAGNOSTICS, INC., Counterclaim Defendant, and ISIS INNOVATION LIMITED, Nominal Counterclaim Defendant.	

I, Farideh Bischoff, declare as follows:

I. Introduction And Summary Of Opinions

1. I am currently Vice President, Translational Research and CLIA Development at Biocept, Inc. in San Diego, California. I am also President and Founder of FZB Consulting, Inc. From various times from July 1994 to September 2010, I held the positions of Associate Professor, Assistant Professor, and Visiting Scientist in the Departments of Obstetrics/Gynecology and Immunology at Baylor College of Medicine in Houston, Texas. I have over 20 years of experience in the development of non-invasive tests within the fields of prenatal and cancer diagnostics.

2. Attached as Exhibit 1 is a copy of my Curriculum Vitae. I have not testified in deposition or at trial in the past four years. I am being compensated for my time spent on this matter at my normal hourly rate of $600. My compensation is not dependent on the outcome of this case.

3. I have been retained by Ariosa Diagnostics, Inc. ("Ariosa") and asked to provide opinions regarding whether Ariosa's Harmony Prenatal Test meets each of the limitations of the claims of U.S. Patent No. 6,258,540 that Sequenom, Inc. ("Sequenom") has asserted in its Motion for Preliminary Injunction. I refer to the patent as the '540 patent in this declaration. The '540 patent is attached as Exhibit 2. I have also been asked to provide opinions regarding whether the availability of the Harmony Prenatal Test will have the market for noninvasive prenatal testing.

4. In forming my opinions, I have discussed the Harmony Prenatal Test technology with Dr. Ken Song of Ariosa, and I have reviewed the '540 patent, its prosecution history, Sequenom's Motion for Preliminary Injunction and the declarations in support of the motion (including the Declaration of Dr. Mark I. Evans In Support Of Sequenom, Inc.'s Motion For Preliminary Injunction), the testimony of Dr. Mark Evans from his April 27, 2012 deposition in this case, information regarding Ariosa's Harmony Prenatal Test as described or cited herein, and other materials cited herein.

5. For the reasons set forth below, it is my opinion that Ariosa's Harmony Prenatal Test does not infringe the asserted claims (claims 1, 2, 8, 19-22, 24 and 25) of the '540 patent. It is also my opinion that the availability of the Harmony Prenatal Test will not harm the market for noninvasive prenatal testing.

6. I therefore disagree with the opinions expressed in the Evans declaration regarding the scope of the asserted claims of the '540 patent and whether the Harmony Prenatal Test infringes those claims. I also disagree with Dr. Evans' opinion regarding potential harm to the market for noninvasive prenatal testing.

II. Professional Experience And Qualifications

7. I received a B.S. in Biochemistry with distinguished honors in 1986 from State University of New York, Stony Brook. I received my Ph.D. in 1991 in cancer biology from the University of Texas Graduate School of Biomedical Sciences, Houston. I then completed a Post Doctoral Research Fellowship in 1993 at the University of Texas M.D. Anderson Cancer Center in Houston. I participated in a Fellowship Training Program in Human and Molecular Cytogenetics from 1993 to 1994 at Baylor College of Medicine, Houston, where I was also a Post Doctoral Research Fellow from July 1993 to June 1994.

8. I currently work at Biocept, Inc. ("Biocept"), a San Diego company that specializes in development and commercialization of oncology-based tests, as Vice President, Translational Research and CLIA Development. From April 2007 to July 2009, I was Director, Translational Research and CLIA Development at Biocept. From August 2009 to February 2010, I was Sr. Director of Translational Research and CLIA Development. While at Biocept, I contributed to the experimental design, validation, and commercial launch of a non-invasive whole blood diagnostic for determining fetal RhD genotype. I also lead a team in development of prenatal and oncology applications of FISH, a technique used to locate DNA sequences on chromosomes.

9. I am also the President and Founder of FZB Consulting, Inc., which provides consulting services on methods and strategies for testing of circulating nucleic acids.

10. From July 1994 to September 2010, I worked at the Baylor College of Medicine in Houston, first as an Assistant Professor, then as an Associate Professor in the clinical Department

of Obstetrics and Gynecology, and finally as a Visiting Scientist in the Department of Immunology.

11. I have received multiple honors and awards for my work, including the American College of Obstetrics and Gynecology Annual Meeting Abstract Blue Ribbon Award for my work on a validation study for novel 3D HydroArray technology for rapid prenatal genetic diagnosis, and Research Awards from the Endometriosis Association for my work on the genetics of endometriosis.

12. I have consulted on numerous topics including methodologies for isolation and analysis of cell-free DNA from whole blood, strategies for recovery and analysis of rare fetal cells from maternal blood, and development of a semi-automated microscope platform for non-invasive prenatal screening of trisomy 21.

13. I am a member of a number of professional societies, including the International Society for Prenatal Diagnosis, the American Society of Reproductive Medicine, and the American Society of Human Genetics.

14. I have served on multiple professional committees and boards, including as Chair of the Scientific Advisory Board of the NIH Fetal Cell Study Group, and the Abstract Review Committee of the American Society of Reproductive Medicine. I currently serve on the Executive Steering Committee of the Preimplantation Genetic Diagnosis International Society.

15. I have received multiple grants, including an NIH grant as principal investigator of the molecular nature of fetal DNA in maternal plasma, and an NIH grant as subcontract principal investigator of a simplified semi-automated prenatal screening method using maternal blood.

16. I have been and continue to be a referee for numerous professional journals including Prenatal Diagnosis, Fetal Diagnosis and Therapy, Human Molecular Genetics, and the American Journal of Human Genetics.

17. I have over 120 scientific publications, including articles in *Cell*, *Science*, *American Journal of Obstetrics and Gynecology*, *Fetal Diagnosis and Therapy* and *Prenatal Diagnosis*. (Ex. 1 at 9-16.)

18. I regularly present at scientific conferences around the world on topics including fetal DNA in maternal plasma and prenatal screening for trisomy 21 (Down syndrome).

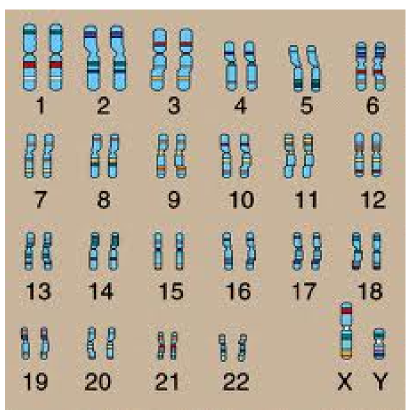
19. I have provided interviews and commentaries to the press, including CNN Live Today, National Public Radio, and US News and World Report, on topics such as prenatal testing.

III. Scientific Background

20. The Ariosa Harmony Prenatal Test is a new test for the determination of risk of certain fetal chromosomal abnormalities called "trisomies," including trisomy 21, which causes Down syndrome. The Harmony Prenatal Test determines this risk by measuring the relative amount (proportion or ratio) of chromosomes in maternal blood samples. In this section, I discuss some of the background that is helpful for understanding chromosomal abnormalities and technological issues in prenatal testing.

A. Chromosomes, Inheritance, and Trisomies

21. Human genetic material is organized in a total of 46 chromosomes. These 46 chromosomes consist of two copies (or pairs) of chromosomes 1 through 22, and two sex chromosomes. The two kinds of sex chromosomes are called X and Y. Females have two X chromosomes, and males have one X chromosome and one Y chromosome. In other words, Y chromosomes occur only in males. A diagram illustrating the 46 chromosomes (for a male) appears below:



22. A fetus normally inherits half of its chromosomes from each parent. One set of 23 chromosomes comes from its mother, and another set of 23 chromosomes from its father. For chromosomes 1 through 22, one of each chromosome is inherited from each of the mother and the

father. For the sex chromosomes, a female fetus inherits one X chromosome from the mother and one X chromosome from the father, and a male fetus inherits the X chromosome from the mother and the Y chromosome from the father. Even though the fetus inherits its chromosomes from its mother and father, it is possible for the fetal chromosomes to be different from the mother's and father's because of spontaneous mutations and recombination events that occur during sperm or egg development.

23. The embryo that grows into a fetus is initially formed by the joining of an egg cell from the mother and a sperm cell from the father; these cells are referred to as germ cells. The egg and sperm each have 23 chromosomes, and they are formed through a process called "meiosis." During normal meiosis, the two copies of 46 chromosomes in the pre-germ cell are equally divided into two different cells, resulting in egg or sperm cells having 23 chromosomes each. When the sperm and egg join, they give rise to an embryo having 46 chromosomes, which is referred to as a "euploid" embryo.

24. Sometimes, however, the separation of a particular pair of chromosomes does not occur (an event called "nondisjunction") and the egg or sperm receives an extra copy of a chromosome or is missing a chromosome. When a sperm of egg having an abnormal number of chromosomes is involved in the fertilization process, it gives rise to an embryo with an abnormal number of chromosomes, referred to as an "aneuploid" embryo. When an egg or sperm contains an extra copy of a chromosome, it will contribute that extra copy of the chromosome to the embryo, so that the embryo has three copies of the chromosome rather than the normal two. Having an extra chromosome is called "trisomy."

25. Down syndrome is in the large majority of cases caused by an extra copy of chromosome 21 (trisomy 21). In other cases, Down syndrome is due to inheriting only part of an extra chromosome 21 rather than an entire extra chromosome 21, generally through translocations of parts of chromosome 21 to other chromosomes. Other trisomies associated with genetic syndromes include trisomy 18, which causes Edwards syndrome, and trisomy 13, which causes Patau syndrome.

26. Nondisjunction events for chromosome 21 usually occur in the mother and not the father. In fact, over 90% of chromosome 21 nondisjunction events occur in the mother's egg. As a result, the extra chromosome 21 in Down syndrome is usually maternally inherited. In addition, nondisjunction rates are higher in older women than in younger women.

B. Nucleic Acids And Nucleic Acid Analysis

27. The chief component of a chromosome is deoxyribonucleic acid ("DNA"), which is the storehouse of genetic information and is a type of "nucleic acid." Another type of nucleic acid is ribonucleic acid ("RNA"), which is generally used by cells in processes that convert the genetic information stored in DNA into proteins.

28. A nucleic acid is a biological molecule that consists of a chain of building blocks called "nucleotides" that are joined together by a backbone of sugar and phosphate groups. Those nucleotide building blocks are the individual components of the genetic information encoded in DNA and RNA. There are four types of nucleotides in DNA; they are typically abbreviated A, C, G and T after their names, adenine, cytosine, guanine, and thymine. In RNA, the types of nucleotides are the same except that uracil, abbreviated U, is used instead of thymine. Because nucleic acids are chains of these building blocks of nucleotides, the order of nucleotides in a nucleic acid is referred to as its "sequence."

29. Regions of DNA that encode proteins are called "genes." A gene for a particular protein will occur at the same location on each of the two copies of a chromosome in a cell (except in the case of a male's X and Y chromosomes, which are not the same chromosome and therefore have regions that do not have the same sequences). Two copies of a gene can have the same sequence, or the sequences can vary, and the individual gene sequences are referred to as "alleles."

30. Nucleic acid analysis can be "qualitative" or "quantitative."

31. Qualitative nucleic acid analysis involves determining whether a particular sequence is present or not.

32. Quantitative nucleic acid analysis involves measuring the amount of a particular nucleic acid. Quantitative methods vary in their performance, and new DNA sequencing-based techniques (discussed in more detail below) have in recent years provided far more accurate

quantitative methods than were available previously. For Down syndrome, highly accurate quantitative analysis is necessary to differentiate the presence of trisomy 21 from the two copies of chromosome 21 found in normal fetuses.

C. Prenatal Testing

33. A variety of prenatal tests are available to pregnant women. Screening tests are blood tests done in the first or second trimester, sometimes along with an ultrasound test. They help evaluate a woman's risk for having a baby with certain birth defects, but they cannot diagnose a birth defect. Screening tests are non-invasive because they only require a blood sample from the mother, rather than fetal cells obtained through an invasive procedure. Each screening test has a certain level of false-positive and false-negative results associated with it.

34. Diagnostic prenatal tests are also available. Amniocentesis is an invasive diagnostic test where a needle is passed through the mother's lower abdomen into the amniotic cavity inside the uterus. Within the amniotic fluid are fetal cells which can be analyzed. Another invasive diagnostic test is chorionic villus sampling ("CVS"). In CVS, a catheter is passed into the developing placenta under ultrasound guidance. This allows sampling of cells from the placental chorionic villi. These cells can then be analyzed. Both amniocentesis and CVS increase the risk of miscarriage and fetal damage.

35. Recently developed technologies for non-invasive tests for trisomies use "next generation" DNA sequencing technologies to analyze cell-free fetal nucleic acids that naturally exist in maternal circulation during pregnancy. These next generation technologies have increased the amount of data available regarding the nucleic acids present in the sample, which has permitted the development of methodologies that can reliably screen such samples for fetal trisomies.

36. For example, Sequenom's MaterniT21 test uses a next generation DNA sequencing technique called massively parallel shotgun sequencing ("MPSS") to test for trisomy 21, 18, and 13. MPSS is a random sequencing approach that produces data from all the chromosomes in the sample, irrespective of their relevance to analysis of a particular trisomy, and evaluates cell-free

DNA without regard to its chromosome of origin. The majority of the sequencing in an MPSS approach is therefore of no use for the analysis of the trisomies of interest.

37. Ariosa's Harmony Prenatal Test, on the other hand, is a chromosome-specific test that uses a directed sequencing approach targeting specific locations on the chromosomes of interest. As a result, the Harmony Prenatal Test uses far less DNA sequencing than MPSS-based tests. The technology behind the Harmony Prenatal Test is described in more detail below.

IV. Legal Standards

38. I have been informed of and have applied the following legal standards in reaching my opinions.

39. I understand that claim construction is the determination of the meaning of patent claims from the perspective of a person of ordinary skill in the relevant art at the time of the claimed invention. The patent claims, properly construed, determine the scope of the invention encompassed by a patent. The patent specification and the public record of its prosecution—the written record of communications between patent applicants and the PTO, called the prosecution history—are important sources of information in claim construction. I understand that if the scope of a claimed invention is narrowed during prosecution to overcome rejections by the PTO, the claims are to be interpreted consistent with that narrowing in the prosecution history. Claim terms should not be interpreted in a manner that would expand the scope of the claimed invention beyond the scope the PTO allowed when issuing a patent.

40. I understand that after the claims are interpreted, they are compared to a product or process in question to determine if the product or process does or does not infringe the claims. A finding of infringement requires a determination that every claim limitation, properly construed, is found in the accused product or process.

41. I understand that a patent claim can be (a) an independent claim with recited claim limitations, or (b) a dependent claim that incorporates the limitations of the independent claim that it references and adds one or more additional limitations. If a product or process is found not to infringe an independent claim because at least one limitation of the independent claim is not found in the product or process, it cannot infringe any dependent claim of that independent claim either.

V. The ’540 Patent And Its Prosecution History

42. The ’540 patent is entitled “Non-Invasive Prenatal Diagnosis” and lists Yuk-Ming Dennis Lo and James Stephen Wainscoat as inventors. I understand that the “Foreign Application Priority Data” listed on the cover page indicates that UK patent application no. 9704444 was filed on March 4, 1997, that an international patent application was filed on March 4, 1998. I understand that a U.S. patent application (Application No. 09/380/696) was filed and prosecuted in the United States Patent and Trademark Office such that, after rejections of pending claims by the patent examiner and amendment of the claims in light of the rejections, the patent application issued on July 10, 2001 as the ’540 patent. I also understand that a continuation patent application (Application No. 09/872,036) was filed but that it was abandoned after the patent examiner repeatedly rejected the broader claims that Drs. Lo and Wainscoat were pursuing in that continuation application.

43. The prosecution history of the application that issued as the ’540 patent is attached as Exhibits 3 to 20, and the prosecution history of the continuation application is attached as Exhibits 21 to 48.

44. When the prosecution of the patent application began in the PTO, the originally submitted claims were directed more broadly to “detecting the presence of a nucleic acid of foetal origin.” For example, original claim 1 recited “A detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample.” Ex. 4, Application at p. 39.

45. The PTO rejected the original claims because, among other reasons, the specification did not enable them. The PTO examiner explained the enablement rejection as follows:

> Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because ***the specification, while being enabling for a method for detecting the presence of paternally inherited fetal DNA*** in maternal plasma after 15 weeks of gestation ***wherein the fetal DNA is from the Y chromosome and for detecting the presence of the RhD gene in maternal plasma from an RhD negative pregnant women*** after 15 weeks gestation, ***does not reasonably provide enablement for a detection method performed on serum or plasma for detecting fetal nucleic acid in general*** at any time during

> pregnancy or associated with disease phenotype in serum. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.
>
> ***The claims are broadly drawn*** to a detection method performed on serum or plasma of a pregnant woman ***to detect any fetal DNA*** at any point in pregnancy.
>
> Ex. 10, Office Action at 5.

46. The instances given above by the examiner of what the specification enabled involve known nucleic acid or DNA sequences inherited exclusively from the father and absent in the mother. First, fetal DNA from the Y chromosome is known to be exclusively paternal because the maternal genome does not have a Y chromosome. Second, the example of an RhD gene from an RhD negative pregnant woman is also an instance of fetal DNA that is known to be exclusively paternal because an RhD negative mother lacks an RhD gene, so it is known that if the RhD gene is detected, it must be exclusively paternally inherited.

47. After the applicants disagreed in their response with the PTO enablement rejection, Ex. 11, Reply at 8, the PTO maintained its rejection of the claims in a Final Office Action because "the specification … does not reasonably provide enablement for a detection method performed on serum or plasma for detecting fetal nucleic acid in general." Ex. 12, Final Office Action at 4. The PTO explained that "the claims remain broadly drawn to the detection of nucleic acids of fetal origin, however, the detection of a maternally inherited nucleic acid from the fetus is unpredictable." Ex. 12, Final Office Action at 10-11. The PTO went on to explain that

> ***The specification explicitly states that "the method of the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother"*** (pg. 4, lines 5-7). As stated in numerous of the papers the concentrations of fetal DNA in maternal plasma may reach 3.4% in early pregnancy and 6.2% in late pregnancy, however, there is a much higher percentage of maternal DNA in late pregnancy. Provided that the skilled artisan obtained a positive result for detection of the nucleic acid, ***it would require undue experimentation [to] determine whether the nucleic acid was a result[] of the maternal DNA found in the maternal plasma or whether in fact the nucleic acid was from the fetus.*** Thus, detection of a maternally inherited nucleic acid would be unpredictable and require undue experimentation.
>
> Thus, for the reasons above and those already of record, the rejection is maintained.

Ex. 12, Final Office Action at 11.

48. The specification statement pointed out by the examiner—"the method of the invention can be applied to the ***detection of any paternally-inherited sequences which are not possessed by the mother***"—appears in the '540 patent at column 2, lines 57-61. After this statement, the patent specification gives the RhD gene example in RhD negative mothers, a circumstance in which the nucleic acid sequence to be detected is not possessed by the mother. '540 patent at 2:62-3:3. The specification then sets forth an example of the beta-globin gene, a gene that has many different mutations in the general population. The specification states that "[p]rovided that the father and mother carry different mutations [in their beta-globin gene sequences], the paternal mutation can be used as an amplification target." '540 patent at 3:4-8. In order to target the paternal mutation, it would be necessary to know what the paternal mutation is prior to the test. Then the specification states generally that mutations in "paternally inherited DNA … can be detected in maternal plasma" but the general method "require[s] the ***prior genotyping*** of the father and mother using a panel of polymorphic markers ***and then an allele for detection will be chosen*** which is ***present in the father, but is absent in the mother***." '540 patent at 3:20-24. "Prior genotyping" refers to determining, before a test is designed and run, the particular genetic sequence at a location of interest in both the father's genome and the mother's genome. According to the specification, information from the prior genotyping is used to choose a particular nucleic acid sequence to which the test will be targeted, and the known nucleic acid sequence must be exclusively paternally inherited and absent in the maternal genome.

49. The other occurrence of "paternally inherited" in the specification appears in the following passage at column 17, lines 35-47:

> We envisage that foetal DNA analysis in maternal plasma and serum would be most useful in situations where the determination of foetal-derived ***paternally inherited*** polymorphisms/mutations or genes would be helpful in clinical prenatal diagnosis (Lo et al. 1994). Examples include foetal sex determination for the prenatal diagnosis of sex-linked disorders, foetal rhesus D status determination in sensitized rhesus negative pregnant women (Lo et al. 1993), autosomal dominant disorders in which the father carries the mutation and autosomal recessive genetic disorders in which the father and mother carry different mutations (Lo et al. 1994), e.g., certain hemoglobinopathies (Camaschella et al. 1990) and cystic fibrosis.

Each of the examples of "determination of foetal-derived paternally inherited polymorphisms/mutations or genes" in this passage involve known nucleic acid sequences inherited from the father and absent in the mother.

50. In addition, each of the experimental examples in the specification involves known nucleic acid sequences that are exclusively paternal.

51. Example 1 is directed to the "[a]nalysis of foetal DNA for sex determination" and discloses that the "detection of Y-specific foetal sequence from maternal plasma, serum and cellular DNA was carried out as described using primers Yl.7 and Yl.8, designed to amplify a single copy Y sequence (DYS14) (Lo et al.1990)." '540 patent at 4:19-5:52. As noted previously, the Y chromosome is exclusively paternal and absent in the mother's DNA. The DYS14 sequence is a known sequence on the Y chromosome.

52. Example 2 is directed to the "[q]uantitative analysis of foetal DNA in maternal serum in aneuploid pregnancies" by "real time quantitative PCR" of "SRY gene" sequences on serum DNA from pregnant women. '540 patent at 5:55-8:50. The SRY gene is known sequence from the Y chromosome and therefore inherited only from the father.

53. Example 3 is directed to "[n]on-invasive prenatal determination of foetal RhD status from plasma of RhD-negative pregnant women." '540 patent at 8:50-11:36. Rh-D negative mothers "lack the Rh-D gene." '540 patent at 9:4. Fetal RhD status is therefore determined using known RhD gene sequence inherited exclusively from the father.

54. Example 4 is directed to detecting "[e]levation of foetal DNA concentration in maternal serum in pre-eclamptic pregnancies" by real time quantitative PCR of SRY gene sequences. '540 patent at 11:38-12:67. As noted for Example 2, the SRY gene is known sequence from the Y chromosome and therefore inherited only from the father.

55. Example 5 is directed to the "quantitative analysis of foetal DNA in maternal plasma and serum" and describes using the SRY TaqMan system on DNA extracted from maternal plasma and serum to determine the amount of fetal SRY gene DNA. '540 patent at 13:1-15:67. Once again, the SRY gene known sequence from the Y chromosome and therefore inherited only from the father.

56. In response to the Final Office Action rejecting the claims that were not limited to paternally inherited nucleic acid (as discussed above), the applicants agreed to narrow their claims. The applicants explained that "the Examiner advised that the claims would be allowable ***if limited to 'paternally inherited' nucleic acid***, since the specification is enabling for detecting paternally inherited nucleic acid in maternal serum or plasma. Such enablement is also indicated in the outstanding Action." Ex. 13, Amendment After Final at 3. Each claim was amended to be specifically limited to "paternally inherited nucleic acid."

57. The PTO examiner raised an additional issue with respect to an amplification step. Specifically, the examiner "believe[d] that an amplification step [wa]s a necessity for the claimed invention." Ex. 14, Interview Summary. Previously, the examiner had raised the issue of "the unpredictability of detecting fetal DNA in plasma before the 15th week of gestation, of detecting paternally inherited non-Y sequences, and the unpredictability of detecting fetal DNA in serum samples." Ex. 12, Final Office Action at 7. The examiner noted that "detecting fetal DNA in maternal plasma samples before the 15th week of gestation … would require the ordinary artisan to ***enrich*** the fetal DNA." Ex. 12, Final Office Action at 7. The specification also addresses enrichment as follows: "A sequence-based enrichment method could also be used on the maternal serum or plasma to specifically enrich for foetal nucleic acid sequences." '540 patent at 2:39-42. Enrichment of the paternally inherited DNA through amplification of that DNA would address the examiner's concern, and a limitation of "amplifying a paternally inherited nucleic acid" was added in an examiner's amendment. Ex. 17, Notice of Allowability at 2-3.

58. The '540 patent subsequently issued with claims limited to detecting paternally inherited nucleic acid of fetal origin and requiring the amplification of paternally inherited nucleic acid. The PTO examiner gave the "reasons for allowance" of the amended claims as follows: "The claims are drawn to a method of detecting paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, by amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample." Ex. 17, Notice of Allowability at 3.

59. The applicants later pursued broader claims in prosecution of a continuation patent application. For example, in that continuing prosecution, the applicants pursued a claim that recited "[a] detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a fetal nucleic acid in the sample by ***detecting nucleic acid which differs qualitatively or quantitatively from that of the maternal genome***." Ex. 27, Reply at 1-2.

60. In that prosecution, the applicants stated the following regarding the previously-issued '540 patent and their reasons for pursuing the continuation application:

> The parent patent 6,258,540 claims in claim 1:
>
> "A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample."
>
> ***This is just one specific example which illustrates the utility of Applicants' claimed invention. Applicants seek in this continuing application to obtain claims that more fully reflect the generality of the invention.*** This is because the term ***"paternally inherited"*** ***<u>does not cover</u>*** ***the cases***: (a) in which ***a gene is maternally inherited, yet the nucleic acid is not (in total) the same in the fetus as in the mother***, and (b) in which ***the gene is altered spontaneously***, for example, in the egg or sperm, i.e. by what appears to be chance or sporadic mutation. Also, it is not always necessary to amplify the nucleic acid in the sample in order to detect the fetal DNA.
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> Ex. 27, Reply at 7.

61. The applicants continued in the same submission to argue for broader claims because "the inventor Lo has demonstrated the applicability of the method to Down's syndrome which is not usually paternally inherited." In other words, the applicants did not believe at the time that the '540 patent claims cover a test for Down syndrome (since it is not usually paternally inherited). The applicants argued that:

> It is immaterial how such a fetal sequence arises; it may be a paternally inherited sequence or it may arise as a result of a spontaneous mutation in either the egg or sperm. Thus the invention is not limited to the detection of paternally inherited DNA. Whilst the application does not provide a specific example of the detection of a specific maternally inherited fetal nucleic acid sequence, it does provide examples of how the invention may be used to screen for a disease that is maternal in origin based on a quantitative assay. The

> additional chromosome 21 present in a Down's affected fetus, whilst not present in the genome in the mother, is usually derived from the egg and is thus maternally inherited.
>
> Ex. 27, Reply at 13-14.

62. In addition, Dr. Lo submitted a sworn declaration as part of the applicant reply quoted above. Similarly suggesting that the '540 patent claims as issued do not cover tests for Down syndrome, Dr. Lo stated that:

> It is not necessary for the success of the method of the present invention that the gene to be detected be paternally inherited. If the mother does not show the disease phenotype, that is sufficient. If the mother can be demonstrated not to have the gene defect for which the fetus is being tested, either through not having the disease phenotype or by prior genetic testing, it matters not whether the gene to be tested is paternally inherited: appearance of the fetal gene in the maternal plasma or serum will indicate its fetal origin.
>
> ***Indeed, the present invention can be used to diagnose Down's syndrome in a fetus***, by carrying out the invention on maternal plasma. The diagnosis depends on detecting an abnormally strong signal from DNA sequence present on chromosome 21 (three copies of which are carried by the fetus). See Poon et al., The Lancet 356, 1819-1820 (November 25, 2000). ***The defect giving rise to an additional copy of chromosome 21 is believed to be maternal in origin. At all events, this [is] a case in which it is irrelevant how it is inherited***, as the additional copy in fetal DNA can be distinguished, if necessary using a marker for a probe for another chromosome.
>
> Ex. 28, Lo Declaration at 9.

63. In short, the applicants understood that the '540 patent claims had been limited—to "one specific example" in their language—and they made clear their desire for broader patent claims, including to claims encompassing a method for detecting maternally inherited nucleic acid and tests for Down syndrome.

64. The PTO rejected the attempt to claim more broadly than the '540 patent claims. In particular, the PTO explained that "the specification does not describe or discuss[] 'detecting the presence of a fetal nucleic acid which differs from that of the maternal genome.'" Ex. 31, Final Office Action at 2. The PTO continued as follows:

> The [applicants'] response on page 7, indicates the continuing application is seeking to obtain claims which more fully reflect the generality of the invention. ***The response has broadened the claims from paternally inherited, which was patented, to detecting the presence of a fetal nucleic acid which differs from that of the***

> ***maternal genome***, because the term "paternally inherited" [does] not cover the cases where (a) the gene is maternally inherited, yet is not the same [in] the fetus as in the mother and (b) the gene is altered spontaneously. The specification does not encompass these two situations in which applicant is seeking to protect. … ***[The] description does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome***. … The concept of "detecting the presence of a fetal nucleic acid which differs from that of the maternal genome" does not appear to be completely supported as part of the originally filed invention. The specification does not appear to have contemplated either spontaneous alterations in the egg and sperm nor differences between maternal and fetal nucleic acids which are argued to be encompassed by the instant claims. Therefore, "detecting the presence of a fetal nucleic acid which differs from that of the maternal genome" constitutes new matter.
>
> …
>
> For the reasons above, in the new matter rejection, the instant specification does not appear to be directed to spontaneous mutations or to differences between maternal and fetal DNA. The specification discusses the paternally inherited DNA.
>
> Ex. 31, Final Office Action at 2-3, 7.

65. Despite these PTO rejections and statements, the applicants continued to pursue the broader claims in multiple exchanges with the PTO. The PTO continued to reject the claims. The PTO reasons for doing so included:

- "Detection of a nucleic acid of interest, associated with a genetic trait, condition or abnormality no[t] present in the pregnant female by amplifying and identifying the presence in the sample of the nucleic acid of fetal origin is unpredictable since there are numerous instances where females may be carriers, but fail to exhibit a genetic trait, condition or abnormality. In order to conclude that the detected nucleic acid is of fetal origin, the nucleic acid could not also be present in the maternal genome. For the reasons above, in the new matter rejection, ***the instant specification does not appear to be directed to*** spontaneous mutations or to ***differences between the maternal and fetal DNA***. The specification explicitly states that 'the method of the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother.'" Ex. 36, Office Action at 8.

- "While the specification may not limit the invention to paternally inherited, the specification does not support the broad scope of nucleic acid of interest, associated with a genetic trait, condition or abnormality not present in the pregnant female. ***The disclosure of paternally inherited nucleic acids in the instant specification does not mean that the specification also supports maternally inherited.***" Ex. 39, Final Office Action at 6.

66. After further prosecution in the continuation application, the PTO issued a Final Office Action rejecting various forms of broader claims. The PTO examiner explained the final rejection as follows:

> The response filed May 13, 2002, on page 7 [quoted above from Ex. 27, Reply], indicates the continuing application is seeking to obtain claims which more fully reflect the generality of the invention. ***The response has broadened the claims from paternally inherited, which was patented, to detecting the presence of a fetal nucleic acid which differs from that of the maternal genome***, because the term "paternally inherited" does not cover the cases where (a) the gene is maternally inherited, yet is not the same as the fetus as in the mother and (b) the gene is altered spontaneously. ***The specification does not encompass these two situations in which applicant is seeking to protect.*** Instead the specification describes "determination of any maternal or fetal condition or characteristic which is related to either the fetal DNA itself or to the quantity or quality of the fetal DNA in the maternal serum or plasma" (page 3 of specification). ***The specification further describes*** the method can be applied to the ***detection of any paternally-inherited sequences which are not possessed by the mother*** and which may be for example gene which confer a disease phenotype in the fetus (page 4). ***This description does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome.***
>
> Ex. 47, Final Office Action at 2-3.

67. After this rejection, there was no further response from the applicants and PTO issued a Notice of Abandonment of the patent application. Ex. 48, Notice of Abandonment. I am informed that there is no public record of any further prosecution of patent applications in the United States related to the '540 patent, and no record of any appeal of the PTO's final rejection. The abandonment of the continuation application therefore represents the applicants' abandonment of their efforts to obtain broader claims than those issued in the '540 patent.

VI. Person Of Ordinary Skill In The Art

68. The '540 patent concerns technology relating to detection of paternally inherited nucleic acid, which involves techniques and procedures that are generally within the fields of molecular biology, molecular genetics and biochemistry.

69. It is my opinion that a person of ordinary skill in the art for the technology of the '540 patent would have a doctoral degree in a field of molecular biology with knowledge of molecular genetics and biochemistry. The person of ordinary skill in the art would also have

experience with the handling, isolation and testing of nucleic acid, including nucleic acid from blood samples.

VII. Non-Infringement Opinions

A. Ariosa's Harmony Prenatal Test

70. Ariosa runs the Harmony Prenatal Test in its laboratory facilities on maternal blood samples collected at physicians' offices and other medical facilities.

71. The Harmony Prenatal Test and test results are described in three recent scientific publications:

(i) Selective analysis of cell-free DNA in maternal blood for evaluation of fetal trisomy, Sparks *et al.*, Prenatal Diagnosis, Vol. 32, pp. 1-7 (2012) (attached as Exhibit 49, and referred to herein as the "Ariosa Prenatal Diagnosis Paper").

(ii) Non-invasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18, Sparks *et al.*, American Journal of Obstetrics and Gynecology, doi: 10.1016/j.ajog.2012.01.030 (2012) (attached as Exhibit 50, and referred to herein as the "Ariosa AJOG Paper").

(iii) Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18, Ashoor *et al.*, American Journal of Obstetrics and Gynecology, doi: 10.1016/j.ajog.2012.01.029 (2012) (attached as Exhibit 51).

72. I have also discussed the Harmony Prenatal Test with Dr. Ken Song of Ariosa. In addition, since the publication of the three scientific publications referenced above, I understand that the Harmony Prenatal Test technology has been extended to include directed sequencing and analysis of trisomy 13 (in addition to trisomy 18 and trisomy 21).

73. The Harmony Prenatal Test involves directed DNA sequencing and analysis of targeted locations ("loci") on certain chromosomes. The directed sequencing and analysis approach stands in contrast to the random sequencing approach used in tests that rely on massively parallel shotgun sequencing ("MPSS"), such as Sequenom's MaterniT21 test. MPSS involves sequencing the DNA in a maternal plasma sample without regard to the chromosomal origin of the sequenced DNA. In other words, in MPSS, maternal plasma DNA from all the chromosomes is

first sequenced and then only a small subset are analyzed to determine, for example, whether the number of DNA sequences from chromosome 21 is unusually elevated. Because chromosome 21 constitutes only about 1.5% of the genome, the MPSS approach requires a large amount of DNA sequencing to generate enough DNA sequence information about chromosome 21 for a determination of whether the amount of that chromosome is elevated. This is inefficient.

74. The Harmony Prenatal Test is a chromosome-specific test (described in more detail below) that avoids the indiscriminate DNA sequencing required by MPSS-based tests such as Sequenom's. As a result, the Harmony Prenatal Test runs using far less DNA sequencing than MPSS-based tests. In particular, the Harmony Prenatal Test requires approximately one million raw reads of DNA sequence per sample (*i.e.*, one million raw reads at the DNA sequencing stage on DNA sequencing machines, before processing of the DNA sequence information and data analysis), whereas MPSS-based approaches involve approximately 25 million raw reads. (Ariosa AJOG Paper at 14.) The reduced amount of DNA sequencing needed for the Harmony Prenatal Test is well within the capacities of currently available DNA sequencing machines, such that cell-free DNA from 96 separate patient samples can be pooled and run at the same time. (Ariosa AJOG Paper at 14.)

75. The Harmony Prenatal Test's directed sequencing approach is called **d**igital **an**alysis of **s**elected **r**egions (DANSR), and the DNA sequencing data from DANSR is analyzed using a novel algorithm developed at Ariosa called **f**etal-fraction **o**ptimized **r**isk of **t**risomy **e**valuation (FORTE).

76. In DANSR, two "assays" are run simultaneously on the cell-free DNA isolated from the maternal blood sample. An assay in this context is a test or analysis of DNA. Blood samples contain cells and extracellular fluid. The cell-free DNA on which the assays are run is DNA that is not inside cells, but rather DNA that exists free of blood cells.

77. The assays target non-polymorphic and polymorphic loci in the cell-free DNA. Non-polymorphic loci are those at which sequences usually do not vary from person to person, and polymorphic loci are those at which sequences often do vary from person to person. The loci used for the non-polymorphic and the polymorphic targeting were determined during the research

and development of the Harmony Prenatal Test at Ariosa, and these loci are now used for each maternal blood sample sent to Ariosa for testing. DANSR does not involve or require any knowledge of the parents' genetic sequences such as through phenotype or prior genotyping of the mother or father associated with any particular maternal blood sample. DANSR also does not require targeting of specific loci based on knowledge of the sequences of the mother or father associated with any particular genetic differences or mutations, such as those discussed in the '540 patent for the beta-globin gene.

78. In the non-polymorphic assay, the test targets 576 non-polymorphic loci on each of chromosomes 18 and 21 for sequencing. (Ariosa AJOG Paper at 6.)

79. In designing the non-polymorphic assay, the loci were selected to have the following properties, which contribute to the performance of the test. First, the loci were at non-polymorphic sequences "unique to the chromosomes of interest," so that other chromosomes were not targeted. (Ariosa Prenatal Diagnotis Paper at 2.)

80. Second, the loci were determined to have "uniform locus-specific oligo melting temperatures." (Ariosa Prenatal Diagnosis Paper at 2.) This means that the loci had DNA sequences that resulted in uniform temperatures at which the oligonucleotides used to target those loci would dissociate (i.e., "melt") from them, which in turn would result in uniform association and dissociation of the test oligonucleotides at the hundreds of loci during the temperature cycling that is a part of the test.

81. Third, the loci were selected to have "minimal complementarity with universal amplification sequences." (Ariosa Prenatal Diagnosis Paper at 2.) This is another consideration in loci selection so that chromosomes other than the target chromosomes were not targeted, and so particular loci on the target chromosomes could be uniquely targeted with minimal noise introduced by other so-called "universal amplification sequences" that occur at various locations in the genome.

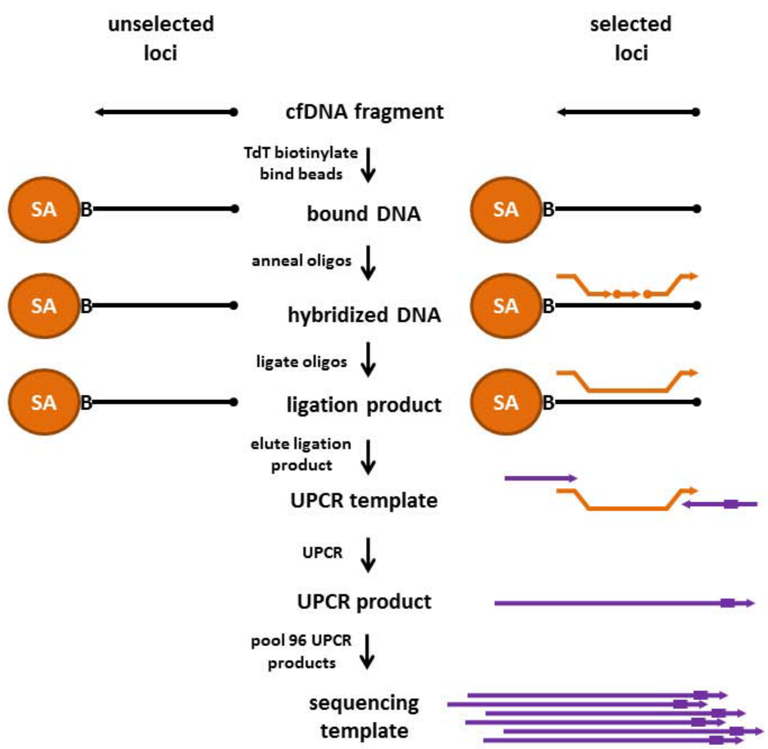
82. Fourth, the loci were selected so that they would "not coincide with known polymorphisms and copy number variants" in order for the assay to be at non-polymorphic sites

on the chromosomes of interest. (Ariosa Prenatal Diagnosis Paper at 2.) None of these selection criteria involved any explicit selection for particular chromosome locations.

83. In the polymorphic assay, the test targets 192 loci on chromosomes 1 through 12. (Ariosa AJOG Paper at 6.)

84. In designing the polymorphic assay, polymorphic loci on chromosomes 1 through 12 were selected. The polymorphic loci have sequences that often differ between individual genomes, so they will often differ between the fetal nucleic acid and maternal nucleic acid in a sample. As the Ariosa AJOG Paper describes it, "[i]nformative polymorphic loci were defined as loci where fetal alleles differ from maternal alleles." (Ariosa AJOG Paper at 8.)

85. DANSR is run by preparing the cell-free DNA fragments from a sample using a proprietary biochemical approach that includes the use of custom-designed oligonucleotides targeting the loci at issue. DANSR is summarized in a schematic from the Ariosa AJOG Paper as follows:



86. The various steps in the DANSR schematic involve cell-free DNA handling and processing. (Ariosa AJOG Paper at 7.) "Anneal oligos" refers to the process of letting the oligonucleotides targeting the loci at issue to bind. "Ligate oligos" refers to a process through

which multiple oligonucleotides annealed at the selected loci are joined chemically using an enzyme called ligase. “Elute ligation product” refers to a process of removing the product of the ligation reaction from the cell-free DNA fragment so that it can be processed further. “UPCR” refers to a polymerase chain reaction step. The overall process leads to DNA products, called “sequencing template” in the schematic, which are then sequenced and run on a sequencing machine. The particular machines currently used at Ariosa for the Harmony Prenatal Test are automated DNA sequencers from Illumina.

87. The DNA sequence data from the sample, as described above, are analyzed as follows.

88. The number of DNA sequences from the non-polymorphic loci on chromosomes 18 and 21 are determined—*i.e.*, the non-polymorphic sequences are counted.

89. The Ariosa AJOG Paper reports the use of a statistical measure called a Z test to assess the proportion of non-polymorphic sequences from each of chromosomes 18 and 21. The Z test evaluates whether there appears to be normal or elevated sequence counts associated with chromosome 18 or 21 in a particular sample as compared to the pool samples run in a batch. (Ariosa AJOG Paper at 7-8.) The Z test was used to evaluate a “training set” of subjects whose aneuploidy status was known. (Ariosa AJOG Paper at 11.)

90. In addition, sequences from the polymorphic loci on chromosomes 1 through 12 are analyzed in order to determine the fraction of cell-free DNA in the sample that is fetal. (Ariosa AJOG Paper at 11.) The fetal fraction determination allows the test to address “a major limitation of the Z Statistic metric” used in the non-polymorphic assay, namely that “samples with low Z Statistic values arise from both euploid samples and aneuploid samples with modest fetal fraction.” (Ariosa AJOG Paper at 12.)

91. The fetal fraction information is used to define the expected chromosome proportions for instances of trisomy versus disomy, and is incorporated into statistical computations in the FORTE algorithm regarding whether a sample has abnormally elevated levels of a chromosome or not. (Ariosa AJOG Paper at 12.) “FORTE … uses fetal fraction information to (1) define expected chromosome proportions for trisomic versus disomic test chromosomes, and

(2) compute the odds that a sample belongs to one group or another." (Ariosa AJOG Paper at 12.) In other words, FORTE addresses samples having a modest fraction of fetal DNA, and the limitations of the Z test, by performing additional statistical analyses using expected chromosome proportions. FORTE also incorporates risks associated with maternal and gestational age to report a risk determination for a particular patient. (Ariosa AJOG Paper at 15.)

B. Asserted Claims Of The '540 Patent

92. I understand that Sequenom has asserted infringement of claims 1, 2, 8, 19-22, 24 and 25 of the '540 patent in its Motion For Preliminary Injunction. The text of each of those claims is set forth below.

93. Claim 1: "A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises

amplifying a paternally inherited nucleic acid from the serum or plasma sample and

detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample."

94. Claim 2: "The method according to claim1, wherein the foetal nucleic acid is amplified by the polymerase chain reaction."

95. Claim 8: "The method according to claim 1, wherein the presence of a foetal nucleic acid from a paternally-inherited non-Y chromosome is detected."

96. Claim 19: "The method according to claim 1, wherein the sample contains foetal DNA at a fractional concentration of total DNA of at least about 0.14%, without subjecting it to a foetal DNA enrichment step."

97. Claim 20: "The method according to claim 19, wherein the fractional concentration of foetal DNA is at least about 0.39%."

98. Claim 21: "A method of performing a prenatal diagnosis, which method comprises the steps of:

(i) providing a maternal blood sample;

(ii) separating the sample into a cellular and a non-cellular fraction;

(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of claim 1;

(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid."

99. Claim 22: "The method according to claim 21, wherein the non-cellular fraction as used in step (iii) is a plasma fraction.

100. Claim 24: "A method for detecting a paternally inherited nucleic acid on a maternal blood sample, which method comprises:

removing all or substantially all nucleated and anucleated cell populations from the blood sample,

amplifying a paternally inherited nucleic acid from the remaining fluid and subjecting the amplified nucleic acid to a test for the Paternally inherited fetal nucleic acid."

101. Claim 25: "A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises

obtaining a non-cellular fraction of the blood sample

amplifying a paternally inherited nucleic acid from the non-cellular fraction

and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid."

C. "Paternally Inherited Nucleic Acid" Limitation of All Asserted Claims

102. A person of ordinary skill in the art would understand the "paternally inherited nucleic acid" claim limitation to mean "known sequence received only from the father, and not fetal sequence which differs from that of the mother." A person of ordinary skill in the art would understand the plain meaning of "paternally inherited" to require knowledge of the father's sequence (whether through a determination of the father's sequence or through knowledge of a particular sequence that could only be from the father, such as a Y chromosome sequence) so that it could be determined whether the fetus received it from the father. Furthermore, the specification and prosecution history provide multiple reasons for why the sequence must be known and received only from the father, and for why the interpretation of "paternally inherited

nucleic acid" should clearly set forth that the term cannot be equated with fetal sequence which differs from that of the mother.

103. First, the specification, as I discuss above in Section V, explains that the sequence for testing must be received only from the father because "[t]he method according to the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother." '540 patent at 2:57-59. In other words, the patent's method of detection is for sequences received only from the father (rather than from the mother or from both parents).

104. In addition, the discussion throughout the specification of detecting gene sequences makes clear that the patent's method is for known sequences received only from the father. The specification passages discuss detecting the following known sequences:

- The beta-globin gene has many known mutations. The specification discusses testing for the father's beta-globin sequence (when the mother's sequence differs from the father's) to see if the father's beta-globin sequence is inherited by a fetus. '540 patent at 3:4-8. This process requires knowing the father's beta-globin sequence.
- The discussion of "prior genotyping of the father and mother," '540 patent at 3:20-24, so that a sequence which is "present in the father, but is absent in the mother" can be chosen for testing is simply a way of saying that the test is for known (through prior genotyping) sequence received only from the father (because it is absent in the mother).
- The DYS14 and SRY gene sequences from the Y chromosome discussed throughout the specification are known sequences, and they are inherited only from the father because only the father has a Y chromosome to pass on to the fetus. Four of the five experimental examples (Examples 1, 2, 4, and 5, as described above in Section V) involve detecting these sequences that are from the Y chromosome. '540 patent at 4:19-5:52; 5:55-8:50; 11:38-12:67; 13:1-15:67.

- The RhD gene for blood type testing is a known sequence that is inherited only from the father when the mother is RhD-negative and therefore lacks an RhD gene. ’540 patent at 2:62-3:3.

105. Second, as summarized in Section V above, the prosecution history clearly indicates that “paternally inherited” was added to the claims during prosecution to narrow them and address the PTO’s rejections of broader original claims encompassing detecting fetal nucleic acids in general. At the outset of prosecution, the claims the applicants sought were directed broadly to “detecting the presence of a nucleic acid of foetal origin.” Ex. 4, Application at p. 39. The PTO rejected the broad claim scope “because the specification … does not reasonably provide enablement for … detecting fetal nucleic acid in general ….” Ex. 10, Office Action at 5. According to the PTO, the specification is “enabling for a method for detecting the presence of paternally inherited fetal DNA … wherein the fetal DNA is from the Y chromosome and for detecting the RhD gene in maternal plasma from an RhD negative pregnant” mother. Ex. 10, Office Action at 5. These are the experimental examples from the specification.

106. After the applicants disagreed in their response with the PTO enablement rejection, Ex. 11, Reply at 8, the PTO maintained its rejection of the claims in a Final Office Action because “the specification … does not reasonably provide enablement for a detection method performed on serum or plasma for detecting fetal nucleic acid in general.” Ex. 12, Final Office Action at 4. The PTO explained that it was maintaining its rejection because “[t]he specification explicitly states that ‘the method of the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother.’” and that “detection of a maternally inherited nucleic acid would be unpredictable and require undue experimentation.” Ex. 12, Final Office Action at 11.

107. The applicants responded by agreeing to narrow their claims, because “the Examiner advised that the claims would be allowable if limited to ‘paternally inherited’ nucleic acid, since the specification is enabling for detecting paternally inherited nucleic acid in maternal serum or plasma. Such enablement is also indicated in the outstanding Action.” Ex. 13, Amendment After Final at 3. This reference to what the PTO found to be enabled refers to the

enablement of detecting fetal DNA from the Y chromosome and for detecting the RhD gene from maternal plasma from RhD-negative mothers—circumstances involving paternally inherited sequences known to be received only from the father.

108. If the ’540 patent claims were interpreted to encompass methods that involve detection of nucleic acids that are paternally inherited but are also maternally inherited (i.e., not only from the father), as Dr. Evans argues, then the interpretation would give the issued ’540 patent claims the scope that the PTO rejected when it was presented with the broader original claims during prosecution of the patent application. This would render the amendment adding “paternally inherited nucleic acid” meaningless. However, interpreting “paternally inherited nucleic acid” to mean known sequence received only from the father is consistent with both the specification and the narrowing amendments to the claims during prosecution that resulted from of the specification’s discussion of “paternally inherited nucleic acid” and lack of support for broader claims to detecting nucleic acid of fetal origin generally.

109. Dr. Evans’ infringement analysis also rests on the premise that the claims encompass circumstances where a fetal nucleic acid differs from the mother’s, because in those circumstances we can conclude that the fetal nucleic acid must have been “paternally inherited,” even if we do not know the father’s nucleic acid sequence. Evans Decl. ¶ 111. This is a false premise, because knowledge of the father’s sequence is required before one knows whether a fetal nucleic acid is in fact inherited from the father. Without that knowledge, a difference between the fetal nucleic acid and the maternal nucleic acid could be for reasons, such as spontaneous mutations, that have nothing to do with inheritance of nucleic acid from the father—reasons that led the PTO to reject the applicants efforts in the continuation application to obtain claims covering detecting fetal nucleic acid that differs from that of the mother.

110. The prosecution history of the continuation application makes these points quite clearly. In that prosecution (as described in detail in Section V), the applicants sought claims explicitly to “detecting nucleic acid which differs … from that of the maternal genome.” Ex. 27, Reply at 1-2. The applicants explained that they were pursuing these broader claims in the continuation because the ’540 patent claims were to “just one specific example” and the term

"paternally inherited nucleic acid" did not cover the circumstances involving nucleic acid that differed from the maternal genome. Ex. 27, Reply at 7.

111. The applicants also made clear in the continuation application that they were pursuing claims lacking the '540 patent's "paternally inherited" limitation because they wanted claims encompassing the detection of an extra copy of chromosome 21 (which causes Down syndrome), a chromosomal abnormality that "is usually derived from the [mother's] egg and is thus maternally inherited." Ex. 27, Reply at 13-14. Dr. Lo confirmed in his sworn declaration his belief that "[i]t is not necessary for the success of the method of the present invention that the gene to be detected be paternally inherited" and that "the present invention can be used to diagnose Down's syndrome." Ex. 28, Lo Declaration at 9.

112. As discussed in Section V, the PTO rejected the repeated attempts by the applicants to claim more broadly than "paternally inherited nucleic acid" because broader claims were unsupported by the specification. The PTO noted that the applicants had "broadened the claims from paternally inherited, which was patented, to detecting the presence of a fetal nucleic acid which differs from that of the maternal genome." Ex. 31, Final Office Action at 2. The broader claims were not patentable because, as the PTO explained, the specification's "description does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome." Ex. 31, Final Office Action at 3. After repeated subsequent attempts by the applicants to obtain broader claims, the PTO maintained the rejections. The PTO stated that "the instant specification does not appear to be directed to … differences between the maternal and fetal DNA." Ex. 36, Office Action at 8. In another rejection, the PTO stated that "[t]he disclosure of paternally inherited nucleic acids in the instant specification does not mean that the specification also supports maternally inherited." Ex. 39, Final Office Action at 6. The applicants abandoned their efforts to obtain broader claims than those issued in the '540 patent. Ex. 48, Notice of Abandonment.

113. From this continuation prosecution history, a person of ordinary skill would understand that "paternally inherited nucleic acid" should not be equated with fetal sequence which differs from that of the mother. That is because, as the PTO stated, the specification's

"description does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome." Ex. 31, Final Office Action at 3. As a result, a person of ordinary skill would understand "paternally inherited nucleic acid" to mean "known sequence received only from the father, and not fetal sequence which differs from that of the mother."

114. I note that Sequenom's expert Dr. Evans does not appear to have relied on the continuation prosecution history. He did not attach it to his declaration, even though he attached the prosecution history of the first application that issued as the '540 patent. I also note that Dr. Evans confirmed at his deposition that he "attached to the declaration the entire prosecution history surround the '540 patent that [he] reviewed." (Ex. 52, Evans Tr. at 59:18-21.) As a result, it appears that Dr. Evans ignored the continuation prosecution history in his analysis, despite its importance for interpreting the asserted claims, and especially its importance in evaluating the interpretation advanced by Dr. Evans for "paternally inherited" (with which I disagree) so that it covers tests for Down syndrome even though the extra chromosome 21 in Down syndrome is in most cases maternally inherited.

115. Under the proper interpretation of "paternally inherited nucleic acid," it is my opinion that the Harmony Prenatal Test does not infringe any of the '540 patent claims asserted by Sequenom in its preliminary injunction motion. All of the asserted claims are limited to a "paternally inherited nucleic acid," and therefore require that the accused method detect known sequence received only from the father, and not fetal sequence which differs from that of the mother.

116. As described above, the Harmony Prenatal Test involves two DNA sequencing assays run simultaneously to determine whether a maternal sample contains abnormally elevated numbers of sequences from chromosome 13, 18 or 21. The Harmony Prenatal Test does not detect *known* sequence received *only* from the father, because Harmony neither requires nor uses any information concerning the genome of the father (or the mother) of the fetus. Instead, the test is run the same way on every sample, regardless of the parental sequences associated with any particular sample, and is not exclusively targeting for paternal sequences. No genetic information regarding the father's sequences is collected or needed to run the Harmony Prenatal Test. This is

in contrast to the ’540 patent’s discussion of detection methods that require knowing the father’s sequence—such as the ’540 patent’s discussion of Y chromosome sequences and exclusively paternal mutations determined through prior genotyping—so that the paternally inherited sequence can be exclusively tested for in the maternal sample. But a test that is exclusively for paternal sequences would not be useful as a Down syndrome test, because trisomy 21 is usually maternally inherited. I note that, when asked whether “a test that is looking for paternally inherited sequences which are not possessed by the mother” would be useful for “Down syndrome cases where the trisomy comes from the mother,” Dr. Evans conceded that such a test “would not be useful for determining Down syndrome inherited from the mother.” (Ex. 52, Evans Tr. at 96:14-97:4.)

117. In short, the two assays in the DANSR procedure are directed toward loci on chromosomes that are received from both the father and the mother, not only from the father. The reason the assays are directed to both is that all copies of the chromosomes of interest need to be counted to determine the risk that the fetus has a particular trisomy (chromosome 21 for trisomy 21, and chromosome 18 for trisomy 18). Dr. Evans agrees that the Harmony Prenatal Test is directed to all the nucleic acid in the sample rather than only the paternally inherited nucleic acid. Ex. 52, Evans Tr. at 198:17-199:12. Because the Harmony Prenatal Test counts all fetal copies of the chromosomes of interest to determine trisomy risk, and not known sequences received only from the father, it does not infringe any of the asserted claims of the ’540 patent.

118. Looking at each of the two assays individually leads to the same conclusion. For the non-polymorphic assay, loci on chromosomes 13, 18 and 21 are targeted (chromosomes that are received from both the father and the mother), and they are counted to determine the proportions of chromosomes 13, 18 and 21 in the sample. The fact that non-polymorphic loci (*i.e.*, loci that usually have the same sequence in a population of men and women) are used means that the sequences are present in and received from both the father and the mother. Furthermore, because all the sequences at these loci are targeted and counted, the non-polymorphic assay does not target sequence received only from the father.

119. For the polymorphic assay, loci on chromosomes 1 through 12 are used (again, chromosomes that are received from both the father and the mother) to determine the fraction of

cell-free DNA in the sample that is fetal. These loci are used because of their polymorphism (*i.e.*, sequences at those locations vary in the population). As discussed above, because polymorphic loci have sequences that often differ between individual genomes, they will often differ between the fetal nucleic acid and maternal nucleic acid in a sample, which permits calculation of the fetal fraction. The fetal fraction information is used in combination with the information about chromosomal proportions from the non-polymorphic assay in the Harmony Prenatal Test's statistical computation of trisomy risk. For this assay at polymorphic loci, the Harmony Prenatal Test does not involve or require any knowledge of the father's sequence, so Ariosa does not know whether a polymorphic sequence at a particular locus is received only from the father.

120. That the polymorphic assay does not involve detecting "paternally inherited nucleic acid" is confirmed by the continuation application prosecution history. In fact, what the Harmony Prenatal Test does involve is "[i]nformative polymorphic loci [that] were defined as loci where fetal alleles differ from maternal alleles." (Ariosa AJOG Paper at 8.) (An allele in this context is sequence variation at the selected loci.) This is exactly what the applicants tried to claim in the continuation, and what the PTO rejected because the specification's "description does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome." Ex. 31, Final Office Action at 3. Dr. Evans agrees that the polymorphic assay is directed to the "differences between fetal alleles and maternal alleles." Ex. 52, Evans Tr. at205:14-206:6, *see also* 123:12-17 ("Q: So in the polymorphic test is it correct to say that it looks for the presence of fetal nucleic acid, which differs from that of the maternal genome? A: Right, and which by implication must come from the father."). For all these reasons, the term "paternally inherited nucleic acid" does not cover fetal sequences that differ from that of the mother. In other words, "paternally inherited nucleic acid" does not encompass the polymorphic loci defined as where fetal sequence differs from maternal sequence. Therefore, the Harmony Prenatal Test does not infringe the asserted claims of the '540 patent.

D. "Amplifying" Limitation of All Asserted Claims

121. "Amplifying" appears in the '540 patent claims before the "paternally inherited nucleic acid" claim language addressed above. A person of ordinary skill in the art would

understand the phrase "amplifying" a paternally inherited nucleic acid in the '540 patent claims to mean "increasing the relative concentration of" paternally inherited nucleic acid as compared to other nucleic acids in the sample, including maternally inherited nucleic acids.

122. Because the "amplifying" limitation was added to the claims during prosecution to address the examiner's concern that without an enrichment step the claimed methods were not enabled, increasing the relative concentration of the paternally inherited nucleic acid compared to other nucleic acids in a sample is a necessary part of the proper construction of the limitation.

123. Furthermore, the specification supports this interpretation. The specification states that "[a] sequence-based enrichment method could also be used on the maternal serum or plasma to specifically enrich for foetal nucleic acid sequences." '540 patent at 2:39-42. A person of ordinary skill in the art would understand the sequence-based enrichment method as a step that is specific for a particular sequence. Specifically enriching a particular sequence increases its relative concentration.

124. Sequenom's expert Dr. Evans agreed at his deposition that amplifying a nucleic acid means enriching it. (Ex. 52, Evans Tr. at 182:8-14 ("Q: Is amplifying DNA the same as enriching DNA? A: Fundamentally."))

125. As further support, Dr. Evans agrees that "a person of ordinary skill in the art would also understand 'foetal DNA enrichment' to have its ordinary and customary meaning of 'increasing the concentration of fetal DNA ***relative*** to the maternal DNA in the sample.'" (Evans. Decl. ¶ 121.)

126. In addition, "amplification" is defined in Stedman's Medical Dictionary (1995) in the area of genetics as "a process for producing an increase in pertinent genetic material, particularly for increasing the proportion of plasmid DNA to that of bacterial DNA." (Ex. 53.) This definition makes clear that increasing the proportion (i.e., increasing the relative concentration) is how a person of skill would understand amplification.

127. In the case of the claim language at issue, "amplifying a paternally inherited nucleic acid" would therefore be understood to mean increasing the relative concentration of known sequence that is received only from the father. The examples in the specification support this

understanding because they consistently involve the use of an amplification procedure (polymerase chain reaction, or PCR) that exclusively targets the known sequences that were received only from the father. As discussed previously, the examples of paternally inherited sequences that were targeted were exclusively paternal beta-globin mutations, ’540 patent at 3:4-8, exclusively paternal mutations determined through prior genotyping of the father and mother, ’540 patent at 3:20-24, exclusively paternal DYS14 and SRY sequences on the Y chromosome, ’540 patent at 4:19-5:52; 5:55-8:50; 11:38-12:67; 13:1-15:67, and exclusively paternal RhD sequence in tests involving RhD-negative mothers. ’540 patent at 2:62-3:3. To target those exclusively paternal sequences, the PCR procedure uses strands of DNA called “primers” that match up with the targeted sequences. The PCR process then produces copies of the sequences that the primers are directed to. Because exclusively paternally inherited sequences are specifically targeted in the specification’s examples, their amplification increases their relative concentration.

128. Under the proper interpretation of “amplifying” in the claims, it is my opinion that the Harmony Prenatal Test does not infringe any of the ’540 patent claims asserted by Sequenom in its preliminary injunction motion. All of the asserted claims require “amplifying a paternally inherited nucleic acid” and therefore require that the accused method increase the relative concentration of paternally inherited nucleic acid. The Harmony Prenatal Test does not include this step, because it does not target known sequence received only from the father and therefore does not increase the relative concentration of any particular sequence received only from the father. As discussed above, the Harmony Prenatal Test’s assays instead target loci on chromosomes inherited from both the mother and the father (and do not target any known sequence received only from the father). All of the sequences at the loci are amplified, whether they are maternally inherited, paternally inherited, or maternal DNA. Consequently, the assays are not set up in any way that would increase the relative concentration of sequence at one locus over another, or, put another way, that would increase the relative concentration of paternally inherited nucleic acid.

129. Sequenom’s and Dr. Evans’ analysis with respect to “amplifying paternally inherited nucleic acid” does not take account of the requirement that the relative concentration of

paternally inherited nucleic acid be increased. Instead, Dr. Evans states simply that the "cell-free nucleic acid – ***including*** paternally inherited nucleic acid of fetal origin – is amplified," (Evans Decl. ¶ 101). Dr. Evans does not address in his declaration the fact that when the cell-free nucleic acid (and not specifically the paternally inherited nucleic acid) is amplified, that process does not increase the relative concentration of paternally inherited nucleic acid. At his deposition, Dr. Evans confirmed his understanding that, in the Ariosa test, the relative concentration of paternally inherited nucleic acid is not increased because all the nucleic acid is amplified. (Ex. 52, Evans Tr. at 186:16-20 ("Q: It [the Ariosa test] amplifies all of the DNA, whether it's inherited from the mother, the father or whether it's anything else, right? A: Yes.")) In other words, under Dr. Evans' interpretation of the claims that reads "amplifying" paternally inherited nucleic acid to encompass amplification of all fetal nucleic acid (including maternally inherited), it does not matter that Harmony amplifies all of the DNA and not known sequence received only from the father. But Dr. Evans' interpretation reads the "paternally inherited" limitation out of the claim.

E. Summary of Non-Infringement Opinions for Asserted Claims

130. Claim 1 of the '540 patent requires "amplifying a paternally inherited nucleic acid" and "detecting the presence of a paternally inherited nucleic acid." For all of the reasons discussed above, the Harmony Prenatal Test does not meet these limitations and does not infringe claim 1.

131. Claims 2, 8, 19, and 20 of the '540 patent are all dependent claims of claim 1 and therefore include all the limitations of claim 1. For all the reasons the Harmony Prenatal Test does not infringe claim 1, it also does not infringe claims 2, 8, 19, and 20.

132. Claim 21 of the '540 patent is also a dependent claim of claim 1 and therefore includes all the limitations of claim 1. For all the reasons the Harmony Prenatal Test does not infringe claim 1, it also does not infringe claim 21. In addition, claim 21 requires "providing a diagnosis." The Harmony Prenatal Test is not a diagnostic test and does not provide a diagnosis. Dr. Evans agrees. Ex. 52, Evans Tr. at 52:7-25. The Harmony therefore does not infringe claim 21 for this additional reason.

133. Claim 22 of the ’540 patent is a dependent claim of claim 21 and therefore includes all the limitations of claim 21. For all the reasons the Harmony Prenatal Test does not infringe claim 21, it also does not infringe claim 22.

134. Claim 24 of the ’540 patent is to a “method for detecting a paternally inherited nucleic acid” and includes the steps of “amplifying a paternally inherited nucleic acid” and “subjecting the amplified nucleic acid to a test for the paternally inherited nucleic acid.” I understand that “detecting a paternally inherited nucleic acid” appears in the preamble and that a preamble can limit a claim when the context of the whole claim suggests that it should be limiting. For claim 24, the reference in the body of the claim to a “test for the paternally inherited nucleic acid” is synonymous with the preamble’s “detecting a paternally inherited nucleic acid.” Dr. Evans agrees with this understanding of “detecting” and “test” in the context of claim 24. Evans Decl. ¶ 139. Therefore, the preamble phrase “detecting a paternally inherited nucleic acid” is a claim limitation, but even if it the Court determines that it is not, the phrase “test for the paternally inherited nucleic acid” in the body of the claim means the same thing. As a result, for all the reasons that the Harmony Prenatal Test does not infringe claim 1, it also does not infringe claim 24.

135. Claim 25 of the ’540 patent requires “amplifying a paternally inherited nucleic acid” and that the method “detect paternally inherited fetal nucleic acid.” These limitations are also requirements of claim 1. For all the reasons the Harmony Prenatal Test does not infringe claim 1, it also does not infringe claim 25.

VIII. Response To Opinion Of Mark I. Evans Regarding Potential Harm To The Market For Noninvasive Prenatal Testing From Ariosa’s Harmony Prenatal Test

136. I have reviewed the declaration of John Stuelpnagel submitted in support of Ariosa’s opposition to Sequenom’s motion for preliminary injunction, including in particular the sections of the Stuelpnagel declaration addressing the assumptions underlying Dr. Evans’ opinion regarding potential harm to the market for noninvasive prenatal testing. I have also reviewed the Welch declaration, Section XI of the Evans declaration, and the materials Dr. Evans relies upon in Section XI of his declaration. I disagree with Dr. Evans for the following reasons.

137. I understand Dr. Stuelpnagel's explanation and description of the validation of the Harmony Prenatal Test as a laboratory developed test ("LDT") in extensive clinical trials. I understand that the Harmony Prenatal Test is not marketed for a particular patient population, and that Ariosa defers to healthcare professionals to decide whether to order the Harmony test for a particular patient and to determine how best to incorporate the results into their clinical practice.

138. As Dr. Stuelpnagel explains, Ariosa has made available information regarding both the completed and ongoing clinical trials for the Harmony Prenatal Test to healthcare professionals who are considering ordering the Harmony Prenatal Test. The Harmony Prenatal Test has been shown to be highly accurate, especially as compared to maternal serum screening tests. The Harmony Prenatal Test also takes into account various risk factors in its statistical analysis, including maternal age, gestational age, and the fetal DNA percentage in the sample. The Harmony Prenatal Test's analytical methods provide individualized patient risk scores for trisomies, whereas Sequenom's MaterniT21 results are provided only as a "positive" or "negative" conclusion. The risk scores reported by Ariosa are more detailed and tailored to the individual patient than those provided by Sequenom.

139. Furthermore, there is no reason to believe that the overall performance of the Harmony test (*i.e.*, its sensitivity and specificity) will be different between average risk and high risk populations, especially since (as pointed out in Ashoor *et al*.) test performance depends on precision and fetal DNA percentage in the sample. There is also no reason to believe that healthcare professionals will fail to understand that the positive and negative predictive values will vary, as a matter of standard statistics, when prevalence of the trisomy of interest varies.

140. Sequenom's decision to limit (at least for now) its MaterniT21 test to pregnant women at "increased risk" or "high risk" of trisomies based on a number of different criteria does not mean that other companies and tests must or should be so limited. Sequenom is apparently limiting its test to these patients because it believes that such a limitation is necessary so that "the community becomes comfortable with the benefits and limitations of a new approach." (Evans Decl. ¶ 151.) While Sequenom is free to introduce its MaterniT21 test to the market in this more limited way if it chooses, I disagree with Dr. Evans' suggestion that Sequenom's approach to the

phased availability of its MaterniT21 test is necessary, or that Ariosa should be prevented from offering the Harmony Prenatal Test.

141. Based on all these facts, including the validation of the Harmony Prenatal Test as a laboratory developed test, and the facts described above and in the Stuelpnagel declaration concerning test performance and statistical measures, the availability of the Harmony Prenatal Test generally and in particular for average risk patients (when healthcare professionals determine it is appropriate) will not harm the market for noninvasive aneuploidy testing.

142. I may supplement my declaration in response to, or otherwise respond to, any additional contentions or evidence raised by Sequenom. I may also supplement my declaration as new information becomes available to me. I may give a tutorial on the scientific background and relevant technical issues, and I may testify regarding my opinions. I may use demonstratives to illustrate scientific background and relevant technical issues, as well as the facts, analysis and conclusions set forth in my declaration, any supplementation of this declaration, and any other rebuttal I give in response to Sequenom's contentions.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on May 14, 2012 in San Diego, California.

Farideh Bischoff

Dr. Farideh Bischoff